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Persistent *Campylobacter jejuni* Infections in Patients Infected with Human Immunodeficiency Virus (HIV)

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We identified *Campylobacter jejuni* infections in four patients infected with the human immunodeficiency virus (HIV); three had persistent and severe *C. jejuni* infections. Multiple isolates obtained from each patient had the same biochemical and serotypic characteristics, indicating recurrent infection rather than reinfection with unrelated strains. Serum antibody responses to *C. jejuni* group antigens by enzyme-linked immunosorbent assay were markedly impaired in the three patients with persistent infection compared with forty-two immunocompetent *C. jejuni*-infected controls and with the HIV-infected patient who readily cleared the organism. One patient was bacteremic; his blood isolate was killed by normal serum but was resistant to his own serum, whereas a simultaneous stool isolate of a different serotype was sensitive. Failure of two patients to eradicate the organism and long-term administration of erythromycin therapy led to the in-vivo development of resistance to this antibiotic, which is most frequently used to treat *C. jejuni* infections.

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CAMPYLOBACTER JEJUNI and closely related organisms are recognized as a cause of diarrheal illness in the United States (1, 2). Typically, infection causes diarrhea, abdominal pain, and fever, which resolve after several days, often without specific antimicrobial therapy (3). Although *C. jejuni* infection occurs commonly in young adults (2) and immunocompetent homosexual men (4), it has been reported infrequently in patients infected with the human immunodeficiency virus (HIV) (5, 6). However, patients with the acquired immunodeficiency syndrome (AIDS) often have chronic diarrheal illnesses, and the etiologic agent frequently is not identified (7). *C. jejuni* infection may be overlooked in patients with AIDS because of an unusual clinical course, lack of sufficient cultures, or the special growth requirements of the organism. Alternatively, it is possible that the immunoregulatory disorders of HIV infection do not predispose to *C. jejuni* infections.

We identified four HIV-infected patients with *C. jejuni* infection. Because three patients had persistent or severe infections and one did not, we examined humoral response to campylobacter infection and correlated these findings with clinical outcome.

Table 1. Clinical Features of Campylobacter Enteritis in Patients Infected with Human Immunodeficiency Virus (HIV)

	Patient 1	Patient 2	Patient 3	Patient 4
Age/sex	67/M	39/M	41/M	42/M
Risk factors for HIV infection	Blood product recipient	Homosexual man	Homosexual man	Homosexual man
HIV antibody by enzyme-linked immunosorbent assay and Western blot	Yes	Yes	Yes	Yes
Other manifestations of HIV-infection	Anemia; progressive dementia	Kaposi sarcoma; *Pneumocystis carinii* pneumonia; herpes proctitis	Kaposi sarcoma *P. carinii* pneumonia; Cytomegalovirus retinitis	Generalized lymphadenopathy
Other enteric infections*	None	None	*Giardia lamblia*	None
Total T4 count†	50	120	50	121
T4/T8 ratio‡	0.1	0.2	0.4	0.8
Total immunoglobulins§				
IgA	1170	694	909	1090
IgG	1370	1100	1730	4290
IgM	58	87	128	152
Prolonged diarrhea	Yes	Yes	Yes	Yes
Fever	Yes	Yes	Yes	Yes; later fever ended
Fecal leukocytes	Yes	Yes	Yes	No
Cleared infection after single course of antibiotics	No	No	No	Yes

* All patients had extensive enteric workups on multiple occasions.
† Normal range for T4 subs ' (per mm³) is 350 to 1600
‡ Normal ratio is greater than 1.0.
§ Normal ranges: IgA, 68 to 291 mg/dL; IgG, 526 to 1421 mg/dL; IgM, 70 to 373 mg/dL.

Materials and Methods

CASE REPORTS

Patient 1. A 67-year-old heterosexual male received 19 units of blood products during coronary artery bypass graft surgery in January 1985 (Table 1). In February 1986 he developed nausea, malaise, and diffuse abdominal pain associated with several watery stools per day. On admission, the patient had a diffusely tender abdomen, and on the fifth hospital day his stone-filled gallbladder was removed; the intraoperative examination was otherwise unremarkable. Postoperatively he developed persistent fevers to 40.3° C associated with abdominal pain and watery stools containing leukocytes. Two stool specimens were negative for *Salmonella, Shigella, Campylobacter,* and ova and parasites, but *C. jejuni* was isolated from bile obtained intraoperatively. Erythromycin, 500 mg every 6 hours, was given intravenously for 8 days, but the patient continued to have fevers, abdominal pain, and diarrhea. Colonoscopic findings showed a 4-cm section of erythematous, friable terminal ileum with a 1-cm ulcer. Microscopically, the mucosa was edematous with prominent lymphoid follicles; crypt abscesses, acid-fast bacteria, viral inclusion bodies, and granulomas were absent. Because the colonoscopic findings were considered to be most consistent with Crohn ileitis, prednisone, 60 mg per day, was given for 3 weeks.

The patient continued to have watery stools and intermittent fevers to 39.1° C. Three stool examinations were negative for *Campylobacter.* Another colonoscopic examination again showed that the entire colon was normal, but the terminal ileum had areas of erythema and nodularity with several discrete deep ulcerations, and there was neutrophilic infiltration of the lamina propria and crypt abscesses. *Campylobacter jejuni* was isolated in heavy growth from cultures of the biopsy specimens; no other bacterial, fungal, or viral pathogens were isolated. Erythromycin, 500 mg orally every 6 hours, was restarted; however, fevers and liquid stools persisted. After 14 days, treatment was changed to tetracycline, 500 mg orally every 8 hours. Colonoscopic examination showed partial healing of the ileal ulcers and cultures were negative for *C. jejuni.*

The patient had progressive lethargy and confusion and died after 117 days in the hospital. At autopsy *Staphylococcus aureus* pneumonia was present, but no opportunistic infections or neoplasm diagnostic of AIDS was seen. A neutrophilic infiltrate, through the lamina propria into the muscularis, was found in the ileum. Gram and Warthin-Starry stains showed curved bacilli on the ileal surface but no microorganisms within or below the mucosa. Culture of the terminal ileum grew *C. jejuni.*

Patient 2. A 39-year-old homosexual male presented in September 1986 with severe *Pneumocystis carinii* pneumonia; a course of prednisone therapy was given for 6 weeks (Table 1). In November he began having up to six watery stools without mucus daily, associated with abdominal cramps and fever to 39.4° C. His stools contained occasional polymorphonuclear leukocytes without blood and culture grew *Campylobacter coli.* Symptoms resolved within 24 hours after beginning therapy with erythromycin, 250 mg orally every 6 hours. Two of three pretherapy blood cultures grew *C. jejuni* that was sensitive to all antibiotic treatments tested. Erythromycin therapy was continued for 21 days, but 9 days after stopping therapy, loose watery stools recurred, and erythromycin-resistant *C. coli* was isolated from stool culture. Tetracycline, 500 mg orally every 6 hours, was begun and symptoms improved. After 4 weeks, tetracycline therapy was discontinued. The patient remained asymptomatic and had four negative stool cultures. He died in October 1987 with progressive wasting.

Patient 3. A 41-year-old homosexual male presented in November 1985 with several complications of AIDS including cytomegalovirus retinitis (Table 1). His medications included 9-(1,3-dihydroxy-2-propoxymethyl)guanine (DHPG), resulting in leukopenia. In June 1986, after having four to five watery stools per day, *Giardia lamblia* infection was diagnosed, and symptoms improved after metronidazole therapy. In August he

developed watery diarrhea with mucus; *C. jejuni* was the only pathogen identified. After erythromycin treatment, 250 mg orally every 6 hours for 1 week, his symptoms resolved. Two weeks later diarrhea recurred and multiply-sensitive *C. jejuni* again was isolated from stool cultures. His symptoms resolved during a 10-day course of erythromycin therapy, but diarrhea recurred 5 days after cessation of therapy, and *C. jejuni* was isolated from stool culture. A 4-week course of erythromycin therapy was given, but the patient continued to have 7 to 10 orange, watery stools with mucus per day. *Campylobacter jejuni* isolates were now resistant to erythromycin. After 3 days of therapy with tetracycline, 500 mg orally every 6 hours, the diarrhea stopped. Tetracycline therapy was continued for 2 weeks after which stools were culture-negative. Symptoms recurred after 11 days, and tetracycline-sensitive *C. jejuni* was again isolated from stools. Chronic tetracycline treatment was instituted, and the patient remained asymptomatic. The patient died in April 1987 from progressive respiratory compromise. No postmortem examination was done.

Patient 4. A 42-year-old homosexual male was noted to be HIV-antibody positive in April 1986 (Table 1). Subsequently, he developed intermittent diarrhea that lasted 11 months; generally, he had 6 to 10 watery stools per day for 3 weeks each month. Sigmoidoscopic findings were consistent with Crohn disease; he received treatment with sulfasalazine without apparent improvement of symptoms. In April 1987 he was admitted to the hospital with lethargy, confusion, and diffuse lymphadenopathy. His sensorium cleared after fluid and electrolyte replacement, at which time he described severe constant watery stools for the week before admission. A complete workup included a computed tomographic scan and lumbar puncture; no abnormal findings were reported. *Campylobacter jejuni,* sensitive to erythromycin, was isolated from stools. He was treated with oral erythromycin therapy for 3 weeks, became asymptomatic, and had three follow-up stool cultures that were negative for pathogens, including *C. jejuni.* His diarrheal symptoms have recurred intermittently for 10 months; his course has been complicated by ascites presumed to be due to hepatitis B.

BACTERIOLOGIC METHODS

Campylobacter organisms were identified to the species level as previously described (8). Susceptibility to 12 antimicrobial agents was assayed by disc susceptibility testing and an agar dilution method (9). Serotyping using heat-stable (Penner system) and heat-labile (Lior system) antigens was done at the Campylobacter Reference Laboratory, Centers for Disease Control, Atlanta, Georgia (10). Isolates were assayed for susceptibility to complement-mediated bactericidal activity present in pooled normal human serum and in each patient's own serum, as previously described (11). Serum specimens from the HIV-infected patients were heated to 56° C for 30 minutes to inactivate HIV, and then a standard quantity of exogenous complement was added before starting the assay (11).

SEROLOGIC METHODS

The HIV-infected patients each had four to nine serum specimens collected throughout their campylobacter infections. Convalescent specimens obtained from 42 healthy adults 3 weeks after they had been orally challenged and infected with *C. jejuni* (12) were used as controls. Negative controls consisted of prechallenge specimens from the same volunteers. *Campylobacter*-specific IgA, IgG, and IgM levels were determined by enzyme-linked immunosorbent assays using surface proteins as described (13). In brief, an acid-extraction of Penner strains 1, 2, and 3 was used as the antigen. After blocking, test serum samples were placed in triplicate wells. The conjugates used were class-specific goat anti-human immunoglobulins (Tago, Burlingame, California). Quantitative determinations for total IgA, IgG, and IgM were done by nephelometry with a Beckman ICS Analyzer II (Immuno Systems Operations, Brea, California).

Results

CHARACTERIZATION OF THE ISOLATES

All isolates obtained from the HIV-infected patients showed typical phenotypic features of *Campylobacter* species; nine were *C. jejuni* and two were *C. coli* (Table 2). The stool isolates were of the same serotype for each patient. The isolates from Patient 1 were intermediately susceptible to erythromycin therapy; this susceptibility remained constant throughout his illness. In contrast, Patients 2 and 3 had original isolates that were susceptible to erythromycin therapy, but during the course of their infection erythromycin-resistant isolates developed. The emergence of erythromycin-resistant isolates correlated with clinical relapse in Patient 3. For Patients 2 and 3, tetracycline therapy was begun when erythromycin-resistant isolates were detected. Patient 3 became asymptomatic while receiving tetracycline therapy; however, when he briefly stopped therapy, *C. jejuni* was again iso-

Table 2. Characterization of the Isolates Obtained from Patients Infected with Human Immunodeficiency Virus (HIV)

Day of Illness	Isolate	Serotype		Culture Source	Minimal Inhibitory Concentration of Erythromycin*	Minimal Inhibitory Concentration of Tetracycline†	Log_{10} Kill‡
		Penner	Lior				
Patient 1							
11	*Campylobacter jejuni*	2	4	Gallbladder	4	1	< 0.05
60	*C. jejuni*	2	4	Ileum	4	1	< 0.05
117	*C. jejuni*	2	4	Ileum	4	2	< 0.05
Patient 2							
9	*C. jejuni*	3	36	Blood	4	4	1.0
9	*Campylobacter coli*	28	59	Stool	4	> 64	1.12
40	*C. coli*	28	59	Stool	> 64	> 64	1.67
Patient 3							
7	*C. jejuni*	3	36	Stool	2	Not determined	0.73
47	*C. jejuni*	3	36	Stool	4	1	1.19
71	*C. jejuni*	3	36	Stool	> 64	1	1.60
114	*C. jejuni*	3	36	Stool	4	1	1.04
Patient 4							
Not determined	*C. jejuni*	16, 50, 43	59	Stool	4	1	< 0.05

* Minimal inhibitory concentration of erythromycin defined in μg/mL as described (9): susceptible, less than 0.5; intermediate, 1 to 4; resistant, greater than 8.
† Minimal inhibitory concentration of tetracycline defined in μg/mL as described (9): sensitive, less than 1; intermediate, 2 to 8; resistant, greater than 16.
‡ Mean bactericidal activity in pooled normal human serum from triplicate determinations, toward isolate after incubation for 60 minutes, expressed as log_{10} kill as described (11): sensitive, 1.0 or greater; intermediate 0.1 to 0.99; resistant, less than 0.1.

lated from his stool culture. An erythromycin-susceptible strain of the same serotype was now isolated. Multiple stool cultures from Patient 3 were repeatedly negative during subsequent long-term tetracycline therapy. Patient 2 also became asymptomatic during tetracycline therapy despite the in-vitro resistance of his stool isolates. He took tetracycline therapy for only 1 month, but has remained asymptomatic for 7 months and stools are *Campylobacter* species-free.

Most *C. jejuni* and *C. coli* strains are susceptible to the bactericidal activity in normal human serum (11). This susceptibility may account for the infrequency of extraintestinal infections due to these species (14, 15). Because Patient 2 was simultaneously infected with two different *Campylobacter* strains, and one invaded the bloodstream and the other did not, we were able to test this hypothesis. Both isolates were readily killed by pooled normal human serum (Table 2). However, whereas the patient's own serum from the ninth day of illness readily killed the stool isolate (1.67 $\log_{10}$ killing), the bloodstream isolate was resistant (less than 0.05 $\log_{10}$ killing). Assay of the patient's sera obtained on later dates showed similar phenomena. All of the isolates from Patients 1 and 4 were resistant to killing by pooled normal human serum (Table 2) and by serum from the respective patients (not shown); blood cultures from these two patients were negative.

SEROLOGIC RESULTS

Compared with specimens obtained from healthy volunteers before and after challenge with *C. jejuni,* serum from the three HIV-infected patients with persistent and severe infections (Patients 1 to 3) showed abnormally low *Campylobacter*-specific IgA, IgG, and IgM responses to their campylobacter infections on most determinations. Patients 1 and 2 showed low levels of specific antibodies throughout their infections. In contrast, Patient 3 showed a significant elevation in his *Campylobacter*-specific serum IgA level twice during the course of his illness, each time coinciding with increased symptoms (Figure 1). *Campylobacter*-specific IgG and IgM levels also rose with the second symptomatic episode, but remained below the mean level seen in volunteers before challenge. Patient 4 was able to produce *Campylobacter*-specific antibody in all three immunoglobulin classes in response to his infection (Figure 1).

All four HIV-infected patients had significantly elevated serum total IgA levels (Table 1). For Patient 1, total IgA levels were greater than threefold normal throughout his hospital course. For comparison, we studied total IgA, IgG, and IgM levels in convalescent serum from 10 healthy adult volunteers who were challenged with *C. jejuni* and became ill; all levels were within the normal range. The ratios of mean optical density of the *Campylobacter*-specific antibody level by enzyme-linked immunosorbent assay to the corresponding total immunoglobulin level further shows that the HIV-infected patients had a relative decrease in *Campylobacter*-specific IgA, compared with the *C. jejuni*-infected immunocompetent subjects (Figure 2). For IgG and IgM, the ratios of *Campylobacter*-specific to total immunoglobulins were not significantly different in the HIV-infected patients and the immunocompetent volunteers.

Discussion

The serotyping studies indicate that campylobacter infection may persist in HIV-infected patients. Both *C. jejuni* and *C. coli* are known enteric pathogens of both immunocompetent and immunodeficient hosts (16, 17). The pathology seen in Patient 1 and the findings of fecal leukocytes in three patients are typical of campylobacter enteritis (1, 3, 16). No other pathogens were found despite multiple studies in each patient. Exacerbation of symptoms in Patients 2 and 3 was associated with *Campylobacter* species in stools, whereas in Patient 2 remission of symptoms was associated with absence of the organism. Although Patient 4 was the only patient able to readily eradicate his infection after antimicrobial therapy, the role of *C. jejuni* infection in his previous prolonged diarrheal illness is unknown. Even though no etiologic agent was isolated from earlier stool examinations, his symptoms improved only after therapy with an antibiotic relatively specific for *C. jejuni*. Thus, it is reasonable to conclude that the diarrheal illnesses in these patients were due to *Campylobacter* species.

Despite nine negative stool cultures in Patient 1, examination of pathologic materials indicated an ongoing *C. jejuni* infection. *Campylobacter jejuni* has special growth requirements but is not difficult to isolate when these requirements are met. It is unclear why we were unable to isolate the organisms from the stools of Patient 1, but this inability suggests that some cases of chronic *Campylobacter* enteritis in immunodeficient patients may present cryptically. Both Patients 1 and 4 had lesions consistent with Crohn disease during the course of their diarrheal illnesses, and both were treated for this condition. However *C. jejuni* has not been implicated in the pathogenesis of the "idiopathic" inflammatory bowel diseases (18). Crohn disease-like lesions in patients with AIDS have been previously reported, but no pathogens were identified (19). Our observations suggest that cultures of biopsy specimens or body fluids for *Campylobacter* species may be necessary in HIV-infected patients with chronic or recurrent diarrhea of unclear cause.

The isolates from these four HIV-infected patients were similar in biochemical characteristics, antimicrobial susceptibilities, and serotypes to isolates found in immunocompetent populations; however, in immunocompetent hosts, *C. jejuni* infections are brief and usually self-limited (3). Immunocompetent patients infected with *C. jejuni* characteristically produce *C. jejuni*-specific immunoglobulins in both serum (20) and intestinal fluids (21), and elevated levels of preexisting *C. jejuni*-specific antibody may protect against symptomatic expression of infection (22). Patients with AIDS frequently have increased levels of serum immunoglobulins (23), perhaps due to polyclonal activation of B cells (24). In contrast, humoral immune response to specific antigens such as pneumococcal capsular polysaccharide (25) or specific infecting agents, such as *Mycobacterium avium-intracel-*

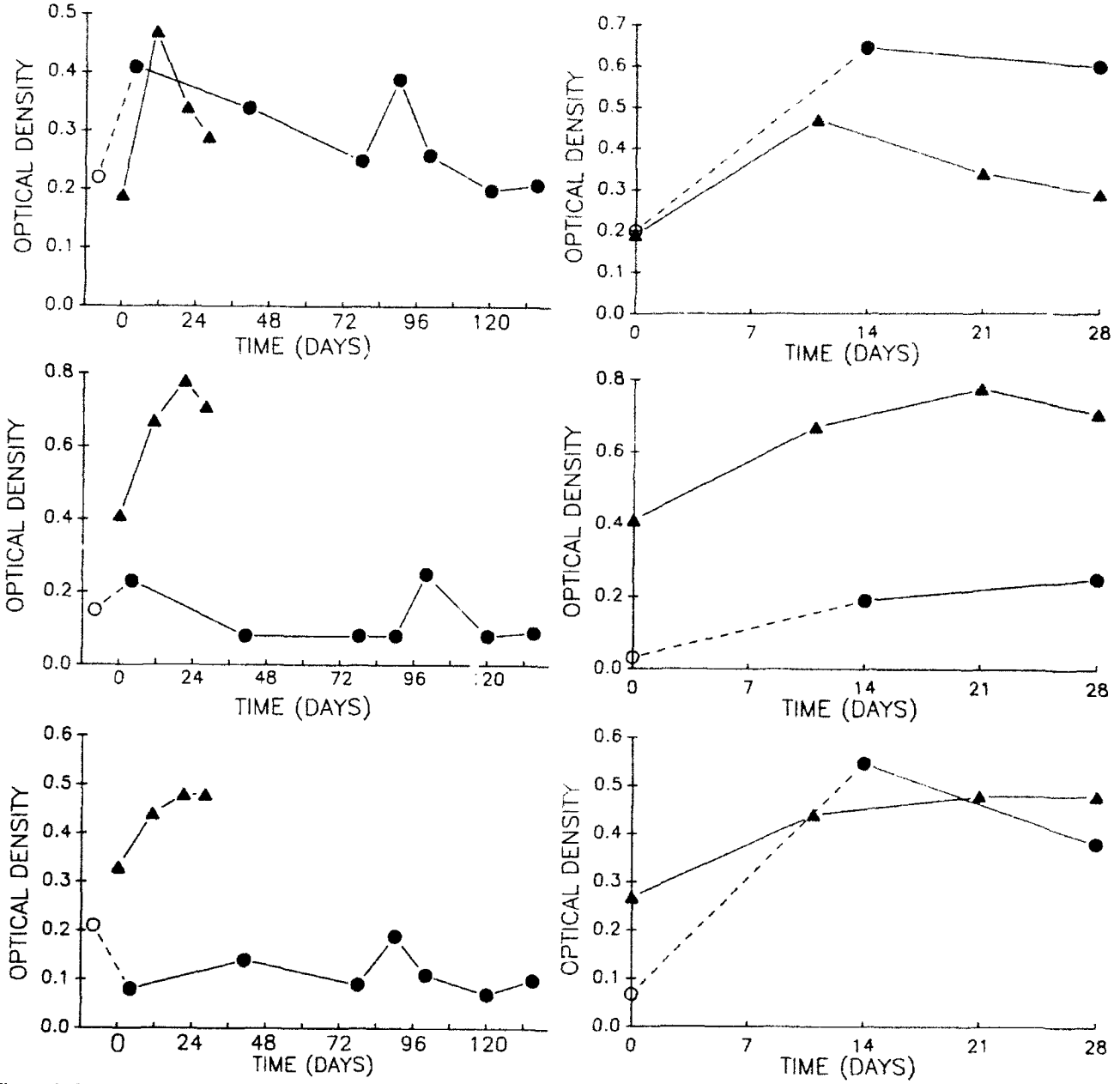

Figure 1. Serum *Campylobacter jejuni*-specific immunoglobulin levels in two patients with the acquired immunodeficiency syndrome (AIDS) (*circles*) and 42 immunocompetent volunteers who became ill after challenge with *C. jejuni* (*triangles*). Top panels: IgA levels; middle panels: IgG levels; bottom panels, IgM levels. The responses of Patient 3 and the volunteers are compared in the left panel; a specimen obtained 65 days before the onset of symptoms (*open circle*) serves as a baseline value for Patient 3. He had a clinical relapse on day 67 of his course. The responses of Patient 4 and the volunteers are compared in the right panels; a specimen obtained 11 months before his first isolation of *C. jejuni* (*open circle*) serves as a baseline value. The solid circle on day 14 represents the value on the day of admission to the hospital (*see* case report). Antibody levels were determined in immunoglobulin class-specific *C. jejuni*-specific enzyme-linked immunosorbent assays; mean optical density values from triplicate determinations are shown on the ordinate.

lulare are deficient in patients with AIDS (26, 27). Our results show that the *Campylobacter*-specific antibody production is defective in HIV-infected patients who cannot readily clear these organisms from the intestinal tract. In contrast, the response in Patient 4 to campylobacter antigens correlated with eradication of the organism. This finding, in combination with the observation that hypogammaglobulinemic patients have severe and persistent *C. jejuni* infections (17), suggests that humoral immunity is of major importance in control of these infections. Our bactericidal studies further support the role of humoral immunity in protecting the bloodstream from intestinal campylobacters (28).

Helper lymphocytes (T4 cells) are depleted in the intestinal mucosa of patients with AIDS (29). All four patients had evidence of cellular immune dysfunction in the form of either opportunistic infections, or by decreased total T4 counts in peripheral blood. The one pa-

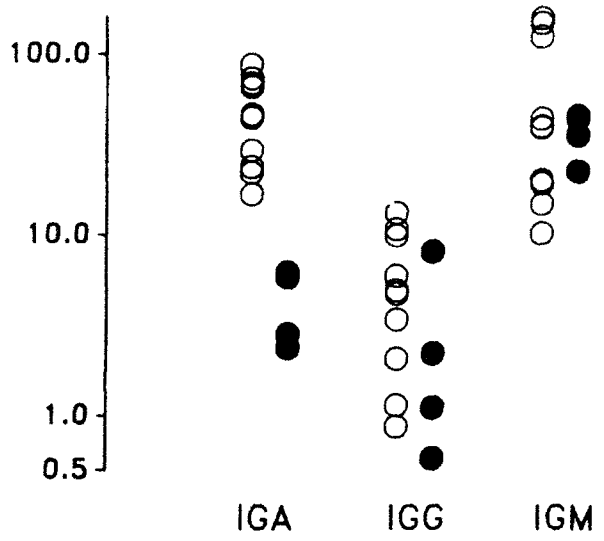

Figure 2. Ratio of *Campylobacter*-specific serum antibody level, measured in units of optical density in immunoglobulin class-specific enzyme-linked immunosorbent assays, to the corresponding total immunoglobulin levels in mg/dL. Ratios obtained from convalescent specimens from 10 immunocompetent volunteers after infection with *C. jejuni* (*open circles*) are compared with the highest ratios attained from each of the four HIV-infected patients during the course of their illness (*closed circles*).

tient who was able to eradicate his *C. jejuni* infection after antibiotic treatment had a low T4 count as well as AIDS-related complex. Thus, cellular immune status alone may not be a determinant of clinical outcome of campylobacter infections. The use of corticosteroids in Patients 1 and 3 and the DHPG-induced leukopenia in Patient 3, may have additionally predisposed these patients to campylobacter infections.

In-vivo development of erythromycin-resistance during campylobacter infection has not been reported previously. Erythromycin-resistant organisms have been isolated from one patient with AIDS (5), and from a hypogammaglobulinemic child with persistent infection (Blaser, MJ. Unpublished data). In those two patients there were no early isolates available to determine whether the organisms had developed in-vivo resistance; however, erythromycin-resistant *C. jejuni* isolates from humans in the United States are uncommon (9). The prolonged nature of the infections requiring antibiotic treatment seen in Patients 2 and 3 may have led to the growth of organisms resistant to the antimicrobial agent used. In Patient 3 the reversion of this isolate to erythromycin susceptibility after the start of tetracycline therapy supports the concept of selective pressure induced by antibiotic treatment. In HIV-infected patients with campylobacter infections, the clinical efficacy of erythromycin therapy should not be assumed.

Patients infected with HIV may have atypical, cryptic, severe, and persistent campylobacter infections and require prolonged antimicrobial therapy. Absent specific humoral immune responses may be associated with failure of the host to clear the organism from the intestine. In-vivo development of resistance to erythromycin, an agent that is bacteriostatic toward *Campylobacter* species (9), is likely a result of selective pressure in hosts unable to clear their infections.

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